Allergy Abstracts

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Asthma and Hay Fever

Reactions of Isolated Human Asthmatic Lung and Bronchial Tissue to a Specific Antigen. Histamine Release and Muscular Contraction. Schild, H. O., Hawkins, D. F., Mongar, J. L., and Herxheimer, H.: The Lancet **2**: 376, 1951.

An 11-year-old child with a history of eczema and asthma since infancy was subjected to a lobectomy because of bronchiectasis. The patient was known to be sensitive to various pollens and inhalants. A chain of bronchial rings taken from the removed lobes were tied together and suspended from a lever in a bath of oxygenated Ringer's solution at 37° C. Addition of specific pollen antigen to the Ringer's solution produced a definite contraction of the bronchial muscle. After washing the bath, a second addition of the same antigen no longer produced a muscle contraction. The muscle was completely desensitized to this antigen. The addition to the bath of other antigens to which the patient was specifically sensitive again produced contractions. After the muscle was desensitized to pollen, it still produced contractions upon the addition of histamine to the bath. When similar preparations of bronchial musculature of nonsensitive patients were exposed to like antigens, no reactions were obtained, although histamine produced definite contractions.

When lung tissue was exposed to allergens, histamine was shown to be liberated by means of bioassay determinations. The amount of histamine released was measured by a diffusion method utilizing the response obtained on guinea pig ileum preparations. "The actual amount of histamine released from 1 Gm. of human lung tissue was greater than that obtained under similar experimental conditions from the lungs of guinea pigs undergoing anaphylaxis." These results seem to indicate that muscle spasm as well as edema is an important abnormal physiological reaction occurring in bronchial asthma.

Antihistamine drugs in very weak dilutions were most effective in blocking the action of histamine upon bronchial muscle. Much stronger concentrations, however, had only a mild effect upon muscular contraction induced by specific excitants. It is suggested that antihistamine drugs are relatively ineffective in preventing the muscle spasm of asthma because of the tremendous amount of histamine liberated at the site of the allergic reaction. The dosage of antihistamine needed to counteract this quantity of histamine approaches its toxic level. The authors conclude that histamine release and muscle spasm are equally important mechanisms in animal anaphylaxis and in human bronchial asthma. R. W.

Cortisone in Asthma. Mitchell, H. S., and Cameron, G.: Canad. M. A. J. **66**: 313, 1952.

Twenty-one patients who had suffered from bronchial asthma for periods ranging from a few months to 49 years were given cortisone, either orally or intramuscularly. Most of the subjects had some degree of emphysema. Nine patients in the group showed positive skin reactions. Approximately 50 per cent of the patients obtained rapid relief, but the improvement was only temporary, lasting from 1 to 12 weeks. Seven patients, most of whom had severe emphysema, failed to improve. Equally effective results were obtained by the oral and the intramuscular administration of the drug. Two hundred milligrams of the drug was given on the first and second day of therapy; thereafter, the dosage was gradually reduced. Three patients in status asthmaticus improved rapidly. Side reactions were minimal, although some patients were kept on maintenance therapy for many months. R. W.

Acetylcholine and Cholinesterase in the Blood of Patients Suffering With Bronchial Asthma. Scudamore, H. H., Vorhaus, L. J., II, and Kark, R. M.: J. Lab. & Clin. Med. **37**: 860, 1951.

The bloods of 14 patients with bronchial asthma were studied for the acetylcholine content of the serum and for the cholinesterase content of the plasma and erythrocytes. Acetylcholine was assayed according to the method of Wait on the isolated clam heart. Cholinesterase determinations were measured by the electrometric method of Michel. The patients ranged in age from 25 to 64 years and had suffered from asthma for periods varying from one to 35 years. In most cases, blood for study was taken during or immediately following an asthmatic attack. The mean acetylcholine level in 8 of the patients was significantly greater than the mean value for healthy adults. The plasma and erythrocyte cholinesterase activity was found to be normal in the entire group. E. W.

Dermatology

An Attempt to Demonstrate Antibodies in Eczematous Contact-Type Dermatitis. Curtis, G. H.: Arch. Dermat. & Syph. **65**: 149, 1952.

Blister fluid was obtained from the vesicles of fresh eczematous reactions in 5 patients, of whom 3 were sensitive to beryllium compounds, one to p-amino-benzoic acid, and one to 2-4 dinitrochlorbenzene. The vesicle fluid was injected intracutaneously into normal recipients. From 48 to 96 hours later, patch tests with the corresponding allergens were performed on the prepared sites. Control tests on unprepared sites were applied in all recipients. Negative reactions were obtained at the prepared sites and at the

control sites. Thus, attempts to demonstrate passive transfer antibodies in allergic eczematous contact dermatitis by the Urbach-Koerngstein technique were unsuccessful.

Proteins extracted by ultrasonic radiation and/or homogenization from split thicknesses of skin obtained from the donors were also used for passive transfer. A specimen of tissue was taken from normal skin and from the eczematized skin of each patient. The extracts were injected intracutaneously in normal recipients; after 48 or 96 hours, patch tests were made with the corresponding allergens. All tests gave negative results. It was concluded that, in whatever manner eczematous sensitization is acquired by the epidermis, the substance which reacts with allergen is an essential part of the chemical composition of the cellular protoplasm and, under the conditions of these experiments, could not be separated as a distinct antibody. C.

Contact Dermatitis Due to N-Ethyl-O-Crotonotoluide Ointment (Eurax). Bereston, E. S.: Arch. Dermat. & Syph. **65**: 100, 1952.

Typical lesions of contact dermatitis appeared on the ears, cheeks, chin, and neck of a female patient 24 hours after the application of Eurax ointment to her ears for an acute exacerbation of a chronic recurrent eczema.

One week after the lesions had subsided, patch tests were performed with the ointment, the ointment base, and the active chemical of Eurax. A four-plus reaction was obtained to the Eurax ointment within 48 hours, a one-plus reaction to the ointment base in 48 hours, and a four-plus reaction to the active chemical in 72 hours. Eurax ointment contains 10 per cent N-ethyl-o-crotonotoluide in a polyethylene glycol (carbowax) base and is used as a scabicide and antipruritic ointment.

Condensation Plastics: Their Dermatological and Chemical Aspects. Morris, G. E.: Arch. Indust. Hyg. & Occ. Med. **5**: 37, 1952.

The incidence of dermatitides among workers in the plastic industry has increased more than fivefold in the past 12 years. The dermatitis encountered in this group of individuals results from exposure to the raw materials and intermediary chemicals formed in the process of manufacturing the plastics. The completely polymerized finished materials are dermatologically inert. F.

Treatment of Atopic Dermatitis With Cortisone. Sternberg, T. H., Newcomer, V. D., and Linden, I. H.: J. A. M. A. **148**: 904, 1952.

Cases of atopic dermatitis treated with cortisone, 200 or 300 mg. per day, responded within 24 to 48 hours and cleared maximally in the next 7 to 14 days. When dosage was slowly decreased to 75 or 100 mg. per day, or when the time interval between adequate maintenance doses was increased, symptoms promptly recurred. Tapering off the cortisone and substituting corticotropin kept the lesions under control until such time as the corticotropin was withdrawn. Readministration of cortisone on subsequent occasions was always equally beneficial. Oral and intramuscular administration of the hormone gave comparable results. Local application of the medication was ineffective. Since prolonged high doses of cortisone are required to maintain remissions, the drug should be administered only in those instances of acute exacerbations of atopic dermatitis which cannot be controlled by other methods. F.

Cutaneous Lesions of Allergic Granulomatosis. A Histopathologic Study. Strauss, L., Churg, J., and Zak, F. G.: J. Invest. Dermat. **17**: 349, 1951.

Twelve cases of allergic granulomatosis of the skin were studied. Most of the patients gave a positive history of allergy, ran a febrile course, had a high blood eosinophilia, and had systemic lesions suggesting disseminated vascular disease, such as periarteritis nodosa. Several of the patients died and, at autopsy, granulomatous involvement of the vital organs was observed. None of the skin nodules examined showed necrotizing arteritis. Dermal lesions were either nodular, hemorrhagic, erythema multiforme-like, or a combination of all 3 types. A typical granuloma histopathologically contained "a central core of disintegrating fibers and cells, surrounded by radially arranged histiocytes and giant cells, and lying amidst inflammatory exudate rich in eosinophils." The authors suggest that the presence of skin nodules is more indicative of allergic granulomatosis than of periarteritis nodosa. R. W.

Studies on the Peripheral Vascular Physiology of Patients With Atopic Dermatitis. Eyster, W. H., Jr., Roth, G. M., and Kierland, R. R.: J. Invest. Dermat. **18**: 37, 1952.

A study was made of the alterations in skin temperatures resulting from exposing subjects to an environmental temperature of 25.5° C. (78° F.) then moving them to a temperature of 20° C. (68° F.) for one hour, and subsequently exposing them to 32° C. (89.6° F.) for one hour. Three groups of patients were studied: one group suffered from atopic dermatitis; a second group had various other dermatoses; and a third group which served as controls had normal skins. Both food and medication were withheld from the subjects for 15 to 20 hours prior to the experiment and all the patients had basal metabolic rates done on the same day on which the temperature studies were made. Patients with atopic dermatitis had a more rapid rate of cooling than normal persons in the cool environment and a delayed rate of warming in the warm environment. If the disease was manifest, the season of the year had little influence on the amount of vasoconstriction measured in the tests. Twenty-one of the 24 patients with atopic dermatitis gave a significant hyperactive type of response to a cold pressor test. The nail fold capillaries of 7 patients with atopic dermatitis were studied by means of a high-powered microscope and were found to be normal. Several patients with atopic dermatitis were given intracutaneous injections of 0.1 c.c. of histamine 1:100,000. No flare response was observed following these injections, but no mention is made as to whether these tests were performed on normal or actively diseased skin. The basal metabolic rate was occasionally below normal in the patients with atopic dermatitis. The authors conclude that patients with atopic dermatitis appear to have excessive vasoconstriction of the peripheral vascular system. R. W.

Attempts at Passive Transfer of Allergic Eczematous Sensitivity in Man. Baer, R. L., and Sulzberger, M. B.: J. Invest. Dermat. **18**: 53, 1952.

Blood specimens drawn from 27 patients with eczematous contact-type dermatitis were treated according to the Lawrence technique for separating white cells from whole venous blood. After repeated washings in Tyrode's solution, the cell suspension was injected intracutaneously into the recipients at a level deeper than is customary in intracutaneous injections. The total time which elapsed between the withdrawal of blood and the injection of the white cells into the recipient was about 4 hours. Most of the recipients had been patch tested prior to the transfer test to rule out any preexisting allergic

eczematous sensitivity to the various allergens being used. The recipients were all patients with different dermatologic conditions. The skin sites were indurated and red for from 2 to 9 days following the injection of the white cell suspension. A control patch was applied on the flexor aspect of the upper arm each time a patch test was applied to a sensitized site. The control sites had been prepared with Tyrode's solution or cell suspensions obtained from patients known not to be sensitive to the allergen involved in the particular experiment. The patches were left in place from 2 to 7 days and reactions were read from 2 to 9 days following application of the excitant. The passive transfer tests gave completely negative results in 21 of the 27 cases; in 2 cases, the reactions were questionable; and, in 4, the reactions were positive. Three of these 4 positive reactions were obtained with turpentine, the other with ammoniated mercury. Reactions, however, at the control sites were almost as large as those at the test sites. These recipients, when retested from 2 to 8 months after the original transfer test, showed no diminution in sensitivity to the allergen. The authors were unable to decide whether these results indicated a true transfer reaction or an induced sensitivity in the substitutes. Attempts to produce a sensitivity in several control subjects by repeated applications of turpentine for a period of 2 months were unsuccessful. The authors suggest that the white cells of patients with allergic eczematous hypersensitivity to a specific allergen may contain a factor which increases the capacity of normal skin to become sensitized upon exposure to the particular eczematogenic allergen. R. W.

Otorhinology and Ophthalmology

Effects of the Antihistamine Drugs on Tissue Reactions. Pepys, J.: Acta Allergologica **4**: 115, 1951.

Antihistamine drugs were administered orally in either high or low dosage for periods up to 3 weeks to 13 patients with allergic rhinitis and nasal polyposis. Polypi removed under local anesthesia prior to the onset of the treatment served as controls and were compared with later specimens. Comparison of polypi from the 2 groups revealed that the most marked decrease in both the cellular content and eosinophils occurred in the polypi obtained from the group which had received the high dosage. Among the group which had received low dosage, about one-half the cases showed some decrease while, in the other half, there was an unexpected increase in both the cellular content and eosinophils. There was no relationship between the clinical response to treatment and the tissue changes.

Biopsy specimens of skin were removed from patients who were naturally sensitive or passively sensitized and had been tested with specific antigens. These patients were pretreated by the oral administration or local injection of antihistaminic drugs in an attempt to prevent the whealing reaction. The inhibition of the whealing reaction did not affect the occurrence of typical tissue changes usually present in allergic wheals, indicating that the union of antigen and antibody had not been prevented.

Other experiments demonstrated that pretreatment of skin sites with antihistaminic drugs (promethazine) prior to the intracutaneous injection of histamine-dye or allergen-dye mixtures prevented the enhancing effect of histamine and allergic wheals on the diffusion and absorption of substances from the skin. Both procaine and epinephrine had a similar effect. The promethazine and procaine effect was associated with the production of local anesthesia together with abolition of the flare reaction in both instances. The action of the anti-

histaminic drugs on capillary permeability is related to the ability of these drugs to prevent the increased vascular flow resulting from arteriolar dilatation. This effect is probably due to the action of these drugs on nervous tissues.
H.

Miscellaneous Allergies

Effect of Cortisone on Experimental Production of Arteritis by Passive Sensitization. Cohen, S. G., and Moses, C.: J. Lab. & Clin. Med. **37**: 764, 1951.

Rabbits were passively sensitized by the intravenous injection of 0.5 ml. of a rabbit serum containing precipitin antibodies to horse serum. After an incubation period of one-half hour, the animals were challenged with intravenous injections of horse serum 1:100 in successive doses of 1 ml., 2 ml., 3 ml., 4 ml., and 5 ml. administered at fifteen-minute intervals. One-half of the animals had received cortisone acetate 5 mg. per kilogram of body weight intramuscularly every 12 hours for 3 doses prior to sensitization and immediately after the last challenging dose. Twenty-four hours later, all the animals were sacrificed and sections of internal organs were prepared for histologic study. All of the sensitized animals that had not received cortisone developed typical lesions of panarteritis, and periarterial infiltration of eosinophils, lymphocytes, and polymorphonuclear leukocytes, as well as eosinophilic infiltration into the media and intima of the small pulmonary arteries and arterioles. Animals that had received cortisone exhibited less extensive and modified types of lesions consisting of a light periarterial infiltration of lymphocytes in the pulmonary arterioles. Eosinophils were rarely seen in the lesions of this group. The lesions of panarteritis of the pulmonary arteries were not found. The authors offer the suggestion that perhaps cortisone exerts an effect upon the in vivo union of antigen and antibody or that it may influence the tissue response evoked by antigen-antibody reaction.
E. W.

Papular Wasp Sting Eruption. Sonck, C. E.: Acta Allergologica **4**: 1, 1951.

Four days after being stung by a wasp, a 39-year-old man developed disseminated, nonpruritic papular lesions on the trunk and on the inner surfaces of the extremities. These lesions persisted for 4 weeks and resembled papular syphilids. The histological findings are discussed. The author considers the eruption to have been a toxic or allergic reaction caused by the wasp sting.
H.

Allergic Granulomatosis, Allergic Angiitis, and Periarteritis Nodosa. Churg, J., and Strauss, L.: Am. J. Path. **27**: 277, 1951.

Thirteen cases of the clinical syndrome consisting of severe asthma, fever, eosinophilia, and vascular disturbances in various organ systems are presented and discussed. The anatomical changes in all 13 cases consisted of fibrinoid degeneration of collagen, necrosis of eosinophilic exudate, and granulomatous proliferation of epithelioid and giant cells. These changes have been termed "allergic granuloma." The lesions were seen within vessel walls, as in periarteritis nodosa, but were also found in connective tissue throughout the body. The occurrence of extravascular granulomatous changes distinguishes this syndrome from periarteritis nodosa. The frequent occurrence of cutaneous and subcutaneous nodules, which show the typical connective tissue changes in biopsy specimen, is the diagnostic criterion in allergic granuloma. It is suggested that Loeffler's syndrome may represent a more benign form of this syndrome.
J. S.

Polyarteritis Nodosa in Infancy and Childhood. Fager, D. B., Bigler, J. A., and Simonds, J. P.: J. Pediat. **39**: 65, 1951.

Two case histories of polyarteritis nodosa in children with autopsy findings are presented. One child was a 4-month-old boy, the other a 6-year-old girl.

A review of the English literature revealed that among 484 cases reported, the age of onset ranged from 10 days to 89 years. Ninety per cent of the cases recorded occurred after the age of 15 years and the sex ratio was 2 males to one female. The highest incidence of the disease was in the fourth decade. The disease is relatively uncommon in childhood, only 10 per cent of all cases occurring below the age of 15 years. There was no sex variation among children. J. S.

Clinical Use and Abuse of Antihistamines. Mitchell, H. S.: Canad. M. A. J. **66**: 173, 1952.

The present status of antihistamine drugs is reviewed. Except for their value in relieving uncomplicated hay fever, urticaria, and bronchial asthma in infants, they have been a great disappointment. Due to their toxic side reactions, the indiscriminate use of these drugs by factory employees and motorists has created many new industrial and highway hazards. The author stresses the need for more rational and curtailed use of these medications. R. W.

Anaphylaxis

Effect of Cortisone Upon Passive Anaphylaxis in the Guinea Pig. Nelson, R. J.: Proc. Soc. Exper. Biol. & Med. **77**: 589, 1951.

Virgin female guinea pigs were passively sensitized with given amounts of antibody in the form of rabbit antisera to Type III pneumococci. One group of animals received cortisone for 48 hours before and after the sensitizing injection. In another group, cortisone was not administered until 18 hours after the sensitizing injection. Other animals received the cortisone vehicle or normal saline by injection and served as controls. Forty-eight hours after the sensitizing injection, the animals were sacrificed. A strip from the small intestine and from the uterus from the same guinea pig was then tested in a Dale bath with Specific Soluble Substance III as the antigen. Cortisone therapy failed to influence the contractions of uterine strips in all treated animals. Bowel strips from those animals treated with cortisone 48 hours prior to sensitization showed definite inhibition of the contractile response upon addition of antigen. In the animals treated with cortisone after sensitization, there was no inhibition of the contractile response of the bowel strips. Thus, cortisone either interferes with the association of antibody with the smooth muscle of the gut or depresses the cellular function of the gut, but exerts no influence upon the uterine smooth muscle. B. S.

Precipitin Production in Chickens. VII. The Relation Between Circulating Antibody and Anaphylactic Shock. Makinodan, T., Wolfe, H. R., Goodman, M., and Ruth, R.: J. Immunol. **68**: 219, 1952.

Chickens were sensitized intravenously with 20 mg. of beef albumin and then challenged intravenously, from 4 to 15 days later, with a similar amount of antigen. None of the animals showed symptoms of shock. When the initial sensitizing dose was raised to 40 mg. of beef albumin and the animals were

challenged 6 days later with 20 mg. of beef albumin intravenously, shock quickly ensued. When chickens sensitized with 40 mg. of beef albumin were challenged with 20 mg. of human albumin intravenously, no reaction occurred. When these same animals were injected 15 minutes later with beef albumin, all developed shock. The incidence of shock was restudied after varying the amounts of the sensitizing and challenging injections as well as the time interval between these injections. The results suggested that the precipitin content of the blood and the quantity of the stimulating injection are very important factors in determining the anaphylactic response. Anaphylactic response appeared to be much more closely correlated with the antibody titer than with variations in either the sensitization technique or the incubation period. It was concluded that the chicken is a suitable animal in which to study anaphylaxis. R. W.

Anaphylactic Hypersensitivity Induced in Rabbits to Foreign Proteins in Freund's Adjuvant. Kobernick, S. D., deVries, J. A., and More, R. H.: Proc. Soc. Exper. Biol. & Med. **77**: 696, 1951.

Rabbits were sensitized by repeated intramuscular injections of horse serum or bovine gamma globulin in Freund's adjuvant. The adjuvant contained Falba, Bayol F, and dried tubercle bacilli. One week after sensitization, the rabbits were tested intracutaneously with various dilutions of horse serum, gamma globulin, and P.P.D. The reactions obtained at one hour with the foreign protein, P.P.D. and controls were similar and considered to be nonspecific. The reactions to serum reached their maximum size in 24 hours and then began to recede. With undiluted serum, the necrosis of tissue was extensive and the reactions tended to persist for long periods. The reactions to P.P.D. tended to be of the delayed type, reached their maximum intensity in 72 to 96 hours, and persisted at that level until the seventh day. Thus, the type of sensitivity developed to the serum was different from the tuberculin type of sensitivity and was typical of the anaphylactic or Arthus type. This was confirmed by the presence of circulating precipitins in the serum of the treated rabbits and the capacity of the serum to passively transfer sensitivity to these foreign proteins to guinea pigs. These experiments demonstrate that the sensitivity induced in rabbits to foreign proteins incorporated in Freund's adjuvant is of the anaphylactic or foreign protein type. Tuberculin sensitivity developed simultaneously and in no way influenced the quality of sensitivity developed to the foreign proteins. B. S.

Comparison of Leukocyte Changes Produced by Pyrogens and by Anaphylaxis in the Guinea Pig. Bennett, I. L., Jr.: Proc. Soc. Exper. Biol. & Med. **77**: 772, 1951.

Guinea pigs were sensitized with pyrogen-free normal horse serum, diphtheria antitoxin, or crystalline ovalbumin, and were shocked 20 days later. Total and differential leukocyte counts performed before and shortly after the sensitizing injection failed to reveal any significant changes. Within 5 minutes after the shocking injection, however, there was a marked diminution in the circulating leukocytes, especially the polymorphonuclear cells. When anaphylactic shock was not fatal, a leukocytosis was noted at 4 hours. When pyrogenic preparations were injected into guinea pigs, the leukocytic response was similar to that found during anaphylaxis. A different picture was noted when total eosinophil counts were made. The sensitizing injection of antigen produced no change in the eosinophil counts. After the shocking injection of antigen, a striking rise in eosinophils was noted in from 2 to 4 hours. Following

the injection of pyrogenic material, there was a sharp drop in circulating eosinophils which was most marked by the fourth hour. The leukocyte changes after anaphylaxis apparently are not due to pyrogen contamination. B. S.

Pharmacology, Physiology, and Pathology

Further Studies on Mechanism of Increased Capillary Permeability in Inflammation With the Aid of Cortisone and ACTH. Menkin, V.: Proc. Soc. Exper. Biol. & Med. **77**: 592, 1951.

Two factors play a role in producing increased capillary permeability during an acute inflammatory reaction. In the early phase of inflammation, an alkaline exudate, or leukotaxine induces increased local capillary permeability. As the exudate becomes acid in the later stages of an acute inflammatory reaction, another factor, termed exudin, is liberated. This also increases local capillary permeability. Experiments performed on the skin of the abdomens of rabbits showed that adrenal cortical extract and cortisone suppressed the increase in capillary permeability induced by alkaline leukotaxine. However, these hormones were incapable of suppressing the increase in capillary permeability induced by acid exudin. Changing the pH of the leukotaxine or exudin failed to influence the effect of adrenal cortical extract or cortisone on these substances. ACTH had a marked suppressive effect on the increased capillary permeability induced by exudin but only a mild effect on the increased permeability induced by leukotaxine. Exudin appears to be liberated about the time that an acid reaction develops in the inflamed area. Chemical analysis of exudin suggests that it is a dipeptide to which there may be a prosthetic group attached. Exudin is unlike histamine in that it is nondiffusible, fails to contract an isolated segment of guinea pig intestine, and fails to produce the same pattern of tissue staining as histamine. B. S.

The Effects of L-Epinephrine and L-Nor-Ephinephrine Upon Cerebral Circulation and Metabolism in Man. King, B.D., Sokoloff, L., and Wechsler, R. L.: J. Clin. Investigation **31**: 273, 1952.

Subjects used for the study of cerebral blood flow ranged in age from 19 to 50 years. None of the subjects had cardiovascular disease. Cerebral blood flow was determined by the nitrous oxide technique and a wide range of adjunctive measurements were taken. The epinephrine and nor-epinephrine were introduced in a venous infusion. Nor-epinephrine promptly increased blood pressure and slowed the pulse rate. There was little subjective reaction. Cerebral blood flow decreased from 61 to 56 c.c./100 Gm./minute "apparently because of an increase in cerebrovascular resistance from 1.6 to 2.2 resistance units." Cerebral metabolism was not significantly altered. Epinephrine administration induced palpitation, tremor, excitement, a more rapid pulse rate, an increase in blood pressure less than that produced by norepinephrine and increase in cerebral blood flow. Cerebral oxygen consumption increased. An unusually marked increase in cerebral oxygen consumption was noted in a patient with marked anxiety. The authors caution that, under certain circumstances, nor-epinephrine may so decrease blood flow through vital organs as to produce serious affects. K.

Effect of Antihistamine on the Reticulo-Endothelial System; Investigation of the Reticulo-Endothelial Function With the Aid of Radio Active Chromium Phosphate. Gabrieli, E. R.: Nature **168**: 467, 1951.

Eighty white rats, in groups of 10, were injected with various amounts of the antihistamine 'Antasten' (2-phenylbenzylaminomethylimidazol, Ciba,

Switzerland) in 2 equal doses at 30-minute intervals. Fifteen minutes after the last injection, the rats were given an intravenous injection of a colloid in the form of a radioactive chromium phosphate suspension (labelled with phosphorus^{32}). The biological half-life of the radioactive colloid in the circulating blood was determined. It was more prolonged in the animals treated with 'Antasten' than in normal animals and the uptake of the colloid in the reticulo-endothelial system was retarded. Thirty other rats, in groups of 5, were treated with varying doses of 'Antasten.' These and 5 untreated rats were injected with the chromium phosphate preparation and sacrificed 2 hours later. The constant ratio of distribution of radioactive colloids in the liver, spleen, and lungs in normal animals was maintained in the treated rats. It is suggested that 'Antasten' has a significant inhibitory effect on the rate of colloid absorption of the reticulo-endothelial system, but that there is no special predilection for the liver, spleen, or lungs. I. Glazer

Potentiation by Adrenaline of Protective Effect of Cortisone on Histamine Toxicity in Adrenalectomized Mice. Halpern, B. N., Benacerraf, B., and Briot, M.: Proc. Soc. Exper. Biol. & Med. **79**: 37, 1952.

Though normal mice are relatively insensitive to histamine, adrenalectomized mice are histamine sensitive. Sensitivity to histamine was measured by the degree of hemoconcentration, the greater the sensitivity, the greater the hemoconcentration.

When adrenalectomized animals were treated with cortisone they tolerated 5 lethal doses of histamine. Adrenalectomized animals treated with adrenaline tolerated 5 to 10 lethal doses of histamine. When the adrenalectomized mice were treated with both cortisone and adrenaline, they were able to tolerate 50 to 100 lethal doses. Normal mice were not protected against histamine by either cortisone or cortisone and epinephrine. It is thought that these hormones protect the adrenalectomized animals by increasing the resistance of the vascular bed to the toxic effect of histamine on small vessels. B. S.

The Occurrence of Leucocyte-Platelet Thrombosis in Rheumatic Carditis. Stetson, C. A., Jr.: J. Exper. Med. **94**: 493, 1951.

Histologic studies were made on autopsy material from 6 patients who died during a rheumatic fever attack, 6 patients who had had rehumatic fever but in whom the rheumatic process was inactive for 2 weeks before death (although these had had active rheumatic fever within the year), 15 patients who had rheumatic heart disease but no active rheumatic fever for more than 1 year, 3 patients with subacute bacterial endocarditis due to alpha hemolytic streptococcus infection superimposed on rheumatic heart disease of several years' standing, and 16 patients without any present or past history of rheumatic fever. The cardiac sections were studied for typical Aschoff bodies and for leucocyte-platelet thrombi of the type found plugging the blood vessels in Arthus and Shwartzman phenomena. These thrombi were found in the small veins and capillaries of the myocardium, pericardium, subendocardium, adventitia of the aorta and occasionally in the valves of patients dying with active rheumatic carditis. Such thrombi were not found in patients who did not show histologic evidence of active carditis. In 2 of the 3 patients with subacute bacterial endocarditis, typical thrombi were observed and in both of these cases distinct Aschoff bodies were present. There was no consistent correlation between the location of Aschoff bodies and the location of thrombi, although in general those areas of myocardium containing more numerous Aschoff bodies also exhibited more thrombi.

"In the pericardium, leucocyte-platelet thrombi were consistently found in those areas showing evidences of fresh pericarditis and frequently the thrombi appeared to be associated with small focal hemorrhages." It is noted that occasional "granular plugged vessels" have been described by other workers and that rheumatic verrucae have been shown to be composed of masses of blood platelets with fibrin and enmeshed blood cells. "It is suggested that these cellular thrombi may play a role in the pathogenesis of rheumatic carditis." K.

The Local Effect of Cortisone on the Tuberculin Reaction. Vollmer, H.: J. Pediat. **39**: 22, 1951.

The local effect of cortisone on the tuberculin reaction was studied by testing 9 sensitive subjects intracutaneously with a mixture of tuberculin and cortisone. Control tests were made with tuberculin alone. When compared to the reaction obtained with tuberculin alone, the reaction to the mixture was diminished in all subjects and almost completely inhibited in some of the cases. The induration phase of the skin reaction was more affected than the erythema. It was found, however, that cortisone itself elicited a traumatic skin reaction with a wide surrounding erythema. The erythema component of the skin reaction to the mixture of tuberculin and cortisone was therefore ascribed to the traumatic reaction of the cortisone. When the experiments were repeated in 3 subjects using ACTH instead of cortisone, there was no alteration in the tuberculin reaction.

In 7 of the 9 cases studied, marked itching occurred at the site of the tuberculin injection, but was absent at the site where tuberculin plus cortisone had been injected. In 3 cases, the skin reaction to the tuberculin-cortisone mixture flared up after the fifth day. The explanation for this "rebound" phenomenon is that the tuberculin was temporarily suppressed locally in the skin until the deposit of cortisone had been absorbed, at which time the tuberculin reacted in its usual manner. Local differential white blood counts examined after 48 hours showed a relative decrease of lymphocytes for the reaction to tuberculin plus cortisone as compared to the reaction to tuberculin alone. Skin biopsies were taken after 48 hours on both sites in one subject. The histologic picture of the tuberculin plus cortisone reaction lacked the usual qualitative features of the pure tuberculin reaction. The interpretation placed on this fact was that the histologic response of the skin to tuberculin plus cortisone seemed to be caused by cortisone rather than tuberculin.

The Shick test was inhibited by local cortisone in 5 subjects sensitive to diphtheria toxin. In one case, a "rebound" reaction occurred after the fifth day at the site of injection of diphtheria toxin plus cortisone. Since there is no antigen-antibody reaction involved in the Shick test, this finding would seem to indicate that cortisone causes a diminution in tissue reactivity rather than an alteration in the antigen-antibody reaction. The author points out that it is still undetermined whether the suppression of the tuberculin reaction is due to this same tissue effect or to an additional interference with the antigen-antibody reaction. J. S.

The Fate in Rabbits of Intravenously Injected I^{131}-Iodoovalbumin. Haurowitz, F., and Crampton, C. F.: J. Immunol. **68**: 73, 1952.

Rabbits were given intravenous injections of iodoovalbumin containing about 8 per cent iodine, small parts of which consisted of I^{131}. The rabbits were exsanguinated at various intervals following the injection and the organs removed as quickly as possible for further study. By use of differential

centrifugation, tissue homogenates were separated into nuclear, mitochondrial (large granule), microsomal (submicroscopic particulate), and supernatant fractions in order to determine where within the depository cells the antigen was stored. Samples for counting protein-bound radioactivity were precipitated from the various tissue homogenates by trichloracetic acid. Compounds of low molecular weight were removed from the protein precipitates by various washing procedures.

Study of the blood and organ samples revealed that the antigen disappeared quickly from the blood stream and was deposited in the organs. Within 24 hours, about 90 per cent of the deposited antigen had been eliminated from the organs, although determinant groups of the iodoproteins appeared to be stored in the tissues for a prolonged period of time. Analyses of the subcellular fractions of the organs revealed that the antigen was concentrated in the microsomes of the liver and spleen for a very short time. Thereafter, there was long-term concentration of the antigen in the mitochondrial fraction. The fact that the major portion of the antigen was always found in the cytoplasmic granules would seem to indicate that the antigen molecules, in spite of their colloidal properties, were able to penetrate cellular membranes. From these experiments, the authors are not able to conclude whether the microsomes carry the antigen to the mitochondria or whether the microsomes by mutual aggregation or growth develop into mitochondria. It is suggested that immunity and continued antibody formation are due to the prolonged retention of antigen at sites where antibodies are formed and that antibody formation is a cytoplasmic phenomenon occurring in the presence of the antigen. R. W.

Antihistamines and Thyroxine Metamorphosis in Tadpoles. Hahn, P., and Poupa, O.: Nature **167**: 84, 1951.

Four groups of tadpoles were treated with thyroxine, antihistamine (benzhydryl-B-piperodinoethylether hydrochloride—Spofa III 101), and a combination of the two. After 4 weeks of treatment, it was observed that the antihistamine treatment inhibited the effect of thyroxine and slowed the spontaneous metamorphosis of the treated tadpoles. H.

The Effect of Sodium Pentobarbital on the Toxicity of Certain Antihistamines. Way, E. L., and Herbert, W. C.: J. Pharmacol. & Exper. Therap. **104**: 115, 1952.

White mice were injected intraperitoneally with a median lethal dose (LD_{50}) of Pyribenzamine, Benadryl, Chlortrimeton, or Thephorin. Some of the mice were pretreated with sodium pentobarbital. Another series of mice and also rats received LD_{80} doses of the same antihistamines and were treated with sodium pentobarbital as soon as central nervous system overstimulation appeared. Both pre-treatment and treatment at the first sign of stimulation reduced the death rate from antihistamines. Animals treated after the development of a convulsive seizure rarely recovered. Sodium pentobarbital did not protect rats against Chlortrimeton toxicity, although rats were protected against the other antihistamines when they were injected intraperitoneally. Rats were not protected against orally administered Pyribenzamine or Benadryl. Massive overdosing with any of the antihistamine drugs could not be counteracted by barbiturate administration. Some protection against a median lethal dose was

obtained with a dose of 30 mg. per kg. of sodium pentobarbital, but, when the barbiturate dose was increased to 60 mg. per kg. in an attempt to control convulsions, the animals died of respiratory depression. It is suggested that barbiturate antagonism to antihistamine dosage may be of value clinically, if administered immediately following antihistamine overdosage. K.

Catabolism of I^{131} Labelled Bovine Gamma Globulin in Immune and Non-Immune Rabbits. Dixon, F. J., and Talmage, D. W.: Proc. Soc. Exper. Biol. & Med. **78**: 123, 1951.

Rabbits were immunized either actively with bovine gamma globulin (BGG) or passively with rabbit anti-I^{131} BGG antibody. Immunized and non-immunized rabbits were then injected intravenously with the iodine labelled bovine gamma globulin antigen. Nonprotein bound I^{131} determinations of blood and urine were made at intervals from one to 48 hours after the injection of antigen. The total amount of nonprotein bound I^{131} found in the blood and urine at any given time represented the amount of antigen catabolized. The nonimmunized rabbits catabolized I^{131} BGG with liberation of nonprotein bound I^{131} relatively slowly. A total of 21 per cent was catabolized at 24 hours and 34 per cent at 48 hours. The actively immunized rabbits showed a rapid rate of catabolism of antigen, with 60 per cent being broken down at 6 hours. At 24 hours, 70 per cent of the antigen was catabolized and, at 48 hours, 82 per cent was catabolized. The rate of antigen catabolism in the passively sensitized rabbits was similar to that found in the actively sensitized group. Thus, antibody is the only factor necessary to change slow non-immune antigen catabolism to rapid immune catabolism. It is postulated that the large antigen-antibody complexes stimulate phagocytosis and the phagocytic cells rapidly catabolize the antigen. B. S.

ACTH and Cortisone Aggravation or Suppression of the Febrile Response of Rabbits to Bacterial Endotoxin. Duffy, B. J., Jr., and Morgan, H. R.: Proc. Soc. Exper. Biol. & Med. **78**: 687, 1951.

The febrile responses of rabbits to daily intravenous injections of endotoxin prepared from Shiga dysenteriae during a 2-day test period were studied. One group of rabbits was treated with ACTH or cortisone for 48 hours prior to the injection of the endotoxin and during the 2-day test period. These animals showed a distinct depression of the febrile response as compared to control animals. When smaller doses of ACTH or cortisone were given for 24 hours prior to the test injection and during the 2-day test period, an aggravation of the febrile response was noted as compared to the controls. Failure to appreciate the significance of the timing and dose of these hormones in experiments of this type has resulted in discrepancies in previously reported results. B. S.

Quantitative Antibody Studies in Man. II. The Relation of the Level of Serum Proteins to Antibody Production. Larson, D. L., and Tomlinson, L. J.: J. Lab. & Clin. Med. **39**: 129, 1952.

Quantitative antibody determinations were carried out on the sera of 12 patients with abnormal levels of serum albumin and globulins who had been injected with pneumococcus polysaccharides. There was no apparent relationship between the degree of depression of albumin, the degree of elevation of either globulins or euglobulins, and the amounts of antibody produced. Four patients with multiple myeloma who had low levels of C-antibody and

hyperglobulinemia showed a poor antibody response. No correlation could be established between the ability to maintain an elevated serum gamma globulin level, measured electrophoretically, and the ability to produce antibody. It is noteworthy that "the value obtained for total serum globulins provides no information on the amount of each fraction present." K.

The Response of Serum Gamma Globulin Level and Complement Titer to Adrenocorticotrophic Hormone (ACTH) Therapy in Lupus Erythematosus Disseminatus. Vaughan, J. H. Bayles, T. B., and Favour, C. B.: J. Lab. & Clin. Med. **37**: 698, 1951.

In 4 patients with disseminated lupus erythematosus, it was found that activity of the disease could be roughly correlated with the degree of complement activity and that the duration of the disease was correlated with the degree of gamma globulin content. During ACTH therapy, there was a tendency for the complement titers to rise and for the gamma globulin level to fall. E. W.

Local Hypersensitiveness of the Rabbit Stomach. Jahiel, R., Jahiel, R., and Krakauer, J.: Proc. Soc. Exper. Biol. & Med. **79**: 54, 1952.

Laparotomies were performed on rabbits and their stomachs were sensitized with a subserosal injection of horse serum. After an interval varying from 9 days to 9 weeks, the animals were injected intravenously with the antigen. Control animals received either the sensitizing or challenging injection. The animals were sacrificed at varying intervals after the challenging injection and their stomachs were examined. Localized spontaneous gastric lesions or ulcerations were found in 8 per cent of normal untreated rabbits. Fifty-two per cent of the experimental animals developed gastric lesions. Lesions were found in the stomachs of 12 per cent of the control rabbits. The lesions usually appeared within 24 hours after the shocking injection. They were single or multiple and located within a wide area of the site of the sensitizing injection. The lesions varied in intensity. Some consisted of localized areas of mucosal and submucosal edema with moderate infiltration with lymphocytes, plasma cells, and a few eosinophilic cells. Other lesions showed localized hemorrhagic foci in the lowermost part of the mucosa. The more extensive lesions were necrotic and eroded through the mucosa. Lesions were not found in any other organ of the experimental animal. The authors state that this is the first report of successful local active sensitization of the stomach. B. S.

Effect of Histamine on the Activity of Hyaluronidase. Seelich, F., and Hubl, P.: Nature **168**: 1125, 1951.

The inhibiting effect of heparin upon the action of hyaluronidase on hyaluronic acid was demonstrated by viscosity measurements. The time curves of the reduction of hyaluronic acid in the presence of heparin did not change by addition of histamine. I. Glazer

Miscellaneous

Effect of ACTH and Cortisone on Phagocytosis. Crepea, S. B., Magnin, G. E., and Seastone, C. V.: Proc. Soc. Exper. Biol. & Med. **77**: 704, 1951.

Ten patients were bled before and after treatment with ACTH or cortisone. Leukocytes separated from the blood were tested for phagocytic

activity with virulent Type I pneumococcus and anti-Type I pneumococcus rabbit serum. The phagocytic activity of the neutrophilic leukocyte decreased in 9 of the 10 patients under treatment with ACTH or cortisone. An increase was observed in the remaining case. This was shown to be due to the development of specific antibody during treatment. The depression of phagocytic activity may account for increased susceptibility to infection during ACTH or cortisone therapy. B. S.

Quantitative Antibody Studies in Man. I. The Effect of Adrenal Insufficiency and of Cortisone on the Level of Circulating Antibodies. Larson, D. L., and Tomlinson, L. J.: J. Clin. Investigation **30**: 1451, 1951.

Pneumococcus polysaccharides Types I and II were injected subcutaneously into 5 patients with characteristic Addison's disease, 4 of whom were receiving desoxycorticosterone. Patients receiving cortisone for rheumatoid arthritis and controls suffering from peptic ulcer or arteriosclerotic heart disease were injected with the same polysaccharides. Serum for antibody determination was withdrawn just prior to immunization and 2 and 4 weeks thereafter. The antibody determinations were carried out on the basis of precipitable nitrogen. Maximal titers were obtained in 2 weeks. The patients with adrenal insufficiency formed antibody as readily as the controls. Both the untreated and the cortisone-treated rheumatoid arthritis patients behaved alike and could not be distinguished from the controls by their antibody response. Two subjects were immunized 2 weeks prior to the administration of cortisone and their serum antibodies were followed at 3-hour intervals after the administration of the drug. No change in antibody level resulted, although these subjects were followed for days. "C-antibody" levels remained fairly constant in all 12 subjects studied. It is suggested that species differences or dosages of cortisone may account for the entirely different effects reported in rabbits. K.

The Systemic Toxic Responses of Patients to Treatment With Streptokinase Streptodornase (SK-SD). Hubbard, W. N., Jr.: J. Clin. Investigation **30**: 1171, 1951.

Twenty-eight patients were treated with 90 local instillations of SK-SD for a variety of conditions. Eleven patients had febrile reactions on 22 occasions. Fever began from 4 to 6 hours after treatment, became maximal at 12 hours, and reached normal in 24 to 48 hours. This was often associated with the presence of albumin, glucose, red and white blood cells, and casts in the urine, and always with blood leukocytosis. Nine others had similarly timed reactions consisting of increased urinary white and red cell concentrations and blood leukocytosis. Erythrocyte sedimentation rates, prothrombin and clotting times, and cephalin flocculation readings were unchanged. No delayed toxicity was observed. No acute affects characteristic of streptococcal disease were noted. The possibility that the reactions might be due to pyrogen activity or to foreign protein reaction is considered. Similar responses were observed in a patient who received a single intravenous injection of typhoid vaccine. K.

Immunologic Groups of Poliomyelitis Viruses. Kessel, J. F., and Pait, C. F.: Am. J. Hyg. **51**: 76, 1950.

Poliomyelitis virus strains from 12 human sources were studied with regard to immunologic grouping. The methods used were confirmatory and included challenge of convalescent immune monkeys, challenge of vaccinated

immune monkeys and neutralization of virus by serum from immune animals. Three distinct immunologic groups were found. Data from other laboratories are presented and discussed. Approximately three-fourths of the viruses tested fell into a single group. Only one specimen of a total of 25 from this and other laboratories has been identified as a member of "Group III." K.

Immunization With Somatic Antigens of C Diphtheriae. Frobisher, M., Jr., and Parsons, E. I.: Am. J. Hyg. **52**: 239, 1950.

Outbreaks of cases of diphtheria which are refractory to antitoxin treatment and which occur in previously immunized persons have led to further study of immunologic strains of diphtheria. Seven-hundred thirty-two guinea pigs were immunized with gravis, mitis, minimus, and Park 8 strains and then were challenged by a mitis, gravis, or minimus strain. One-hundred thirty control animals were also used. Resistance of prepared animals was independent of antiexotoxin formation. Type-specific immune responses were noted in detail. Mitis and gravis strains were the most effective antigens. The avirulent strains of mitis and gravis were less satisfactory for immunization than virulent strains. Minimus antigen was relatively ineffective, especially against homologous challenge. The Park 8 strain, although an excellent elicitor of exotoxin, was the poorest antigen against any of the types, being effective only against the mitis type and being especially ineffective against minimus type challenge. Resistance of all groups of guinea pigs was least effective for the minimus strain challenge. K.

Trypsin-Modified Erythrocytes. Their Use as Test Cells in Acquired Hemolytic Anemia. Rosenthal, M. C., Dameshek, W., and Burkhardt, R.: Am. J. Clin. Path. **21**: 635, 1951.

Abnormal antibodies which play a role in the mechanism of acquired hemolytic anemia were titrated, using washed red cells from a normal individual. The diluents used were saline and 20 per cent bovine albumin. In addition, red cells from the patients and from the control subjects were exposed for 10 minutes to a solution of crude trypsin and were then washed and resuspended in saline. Agglutinations were carried out at 37° C., 22° C., and 3° C. Titers obtained with trypsin-treated cells suspended in saline approached the values obtained with untreated cells suspended in albumin, indicating that trypsinization conferred on the cells the ability to react with "incomplete" agglutinins. The end points of the titration were sharper with trypsinized cells. The effect of trypsin on agglutination was most pronounced at low temperatures and it is recommended that less significance be attached to a high titer of cold agglutinins obtained with the trypsin technique. Spontaneous agglutination of trypsin-treated red cells was observed in one case. Trypsin technique is recommended for easy readability of the reactions, absence of prozone, and economy when used on a large scale. K.